

PATENT COOPERATION TREATY

PCT
NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 February 2001 (01.02.01)	Applicant's or agent's file reference 02559PC
International application No. PCT/IB99/01166	Priority date (day/month/year)
International filing date (day/month/year) 22 June 1999 (22.06.99)	
Applicant HAFEN, Ernst	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:
08 January 2001 (08.01.01)

in a notice effecting later election filed with the International Bureau on:

2. The election was
 was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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Facsimile No.: (41-22) 740.14.35

IB9901166

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

E. BLUM & CO.
Vorderberg 11
8044 Zürich
SUISSE

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Fax: 0041 1 251 67 17

Applicant's or agent's file reference
02559PCInternational application No.
PCT/IB99/01166International filing date (day/month/year)
22/06/1999Priority date (day/month/year)
22/06/1999Applicant
UNIVERSITÄT ZÜRICH et al.

IMPORTANT NOTIFICATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Corrected IPER (see page 3)

Name and mailing address of the IPEA/

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 02559PC	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB99/01166	International filing date (day/month/year) 22/06/1999	Priority date (day/month/year) 22/06/1999	
International Patent Classification (IPC) or national classification and IPC C12N15/00			
Applicant UNIVERSITÄT ZÜRICH et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 08/01/2001	Date of completion of this report 11.12.2001
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lanzrein, M Telephone No. +49 89 2399 7358



INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/IB99/01166

I. Basis of the report

1. With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):
Description, pages:

1-44 as originally filed

Claims, No.:

1-31 as received on 30/08/2001 with letter of 29/08/2001

Drawings, sheets:

1/8-8/3 as originally filed

Sequence listing part of the description, pages:

1-16, as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB99/01166

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c));
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims 1-14, 28-31
	No:	Claims 15-27
Inventive step (IS)	Yes:	Claims 1-14, 28-31
	No:	Claims 15-27
Industrial applicability (IA)	Yes:	Claims 1-31
	No:	Claims

**2. Citations and explanations
see separate sheet**

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB99/01166

Reference is made to the following documents:

D1: Leevers, S. et al.: 'The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth.' EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594, XP000877417 EYNSHAM, OXFORD GB

D2: Berg C A; Spradling A C: Studies on the rate and site-specificity of p element transposition. GENETICS 127, 3, 515-524 (1991), cited in the application

D3: Riesgo-Escobar J. R. et al.: chico, a Drosophila homologue of mammalian insulin receptor substrate (IRS) genes, is required cell-autonomously for cell size. 39th Annual Drosophila Research Conference, 1998: 32, p. a12.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application relates to Drosophila mutants with reduced body or cell size. Mutations or null alleles of *chico* result in reduced body size. The *chico* gene product is a homologue of mammalian insulin receptor substrate (IRS) proteins. Mutant flies are thus useful in screening for compounds interacting with the insulin signalling pathway.
2. **Novelty (Art. 33 (2) PCT).**
 - 2.1 Claims 1-14, 28-31 appear to be novel over the cited prior art. Document D1 shows that ectopic expression of a dominant negative mutant of Dp110 ($DP110^{D95A}$) reduced cell size in the wings (Fig. 3) and eyes (Fig. 4) resulting in smaller wings and eyes. Since the claims are restricted to *chico* mutants, D1 does not affect novelty.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB99/01166

2.2 Claims 15-27 lack novelty over D2. As revealed in the description p. 3-4, *chico*¹ is a synonym for the P element induced mutation *fs(2)4*¹ disclosed in D2. The description states that "two further phenotypes associated with the defect *fs(2)4*¹ could be observed: Homozygous animals are reduced in size and adult flies have increased lipid levels". This statement unambiguously reveals that the genotypes of *fs(2)4*¹ and *chico* are the same. Accordingly, it appears that so far undiscovered (or never reported) phenotypic traits of *fs(2)4*¹ were found.

For assessment of novelty of the product claims, said phenotypic traits are of no relevance. Said traits represent non-distinctive characteristics which do not imply a particular form of the product. Since the known and claimed products are identical in all respects, an objection of novelty arises (cf PCT Guidelines Section IV: III-4.8 and IV-7.6).

The same applies with regards to the sequence data included in claims 6, 7.

As a consequence of the above, D2 is prejudicial to novelty of the product claims 15-27.

3. Inventive step (Art. 33(3) PCT).

Claims 1-14, 28-31 are considered to involve an inventive step within the meaning of Art. 33 (3) PCT.

Said claims concern screening methods using *chico* mutants.

The meeting abstract D3 describes the phenotype of *chico* mutants and reveals the function of the gene product as insulin receptor substrate. However, D3 does neither provide any information regarding the gene locus of *chico* nor does it make a link between *fs(2)4*¹ and *chico*. The information provided in D3 is therefore insufficient for the skilled person to generate *chico* mutants for use in the screening methods of said claims.

Thus, D3 is not an enabling disclosure and is therefore not considered relevant for evaluation of inventive step of claims.

Starting from D2, the skilled person would not have derived the phenotype of the reduced body size and therefore would not have considered the use of the mutant for the screening methods recited in claims 1-14, 28-31.

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/IB99/01166

Re Item VIII

Certain observations on the international application

1. Claims 15-27 are unclear because the subject-matter for which protection is sought is not precisely defined.

In the present draft, claim 15 refers to an "insect mutant having at most one wild type *chico* gene". This can be understood as extending to insects having no *chico* gene at all, i.e. insects which naturally do not have the *chico* gene and have some mutation in another gene. Thus, claim 15 and appending claims 16-27 cover a large group of insect mutants, for which there is no support (Art. 6 PCT) and which is not unambiguously distinguishable from the prior art (Art. 6 and Art. 33 (2) PCT).

2. Claims 1, 2, 4, 5, 12-24, 26-31 are not supported by the description as required by Art. 6 PCT. Said claims refer to mutants of any insect, whereas the examples in the description concern *Drosophila* mutants only. The contribution of the present application clearly belongs to the field of *Drosophila* mutants and does not warrant broadening of the whole concept to all insects.

3. Claims 1-5, 8, 10-18, 21-31 refer to a *chico* mutant. The mutant *drosophila* or insect is specified solely by a name which, however, is meaningless to the person skilled in the art. Although the mutation has been described in the prior art, it has been given other names therein. It is therefore not clear what the subject matter is and the claims are not enabled (Art. 5/6 PCT).

The PCT Guidelines state in Section IV, II-4.16: "The use of proper names or similar words to refer to materials or articles is undesirable insofar as such words merely denote origin or where they relate to a range of different products. If such a word is used, then in order to satisfy the requirements of Article 5, the product must normally be sufficiently identified without reliance upon the word, to enable the invention to be carried out by a person skilled in the art. However, where such words have become internationally accepted as standard descriptive terms and have acquired a precise meaning (for example "Bowden" cable, "Bellville" washer), they may be allowed without further identification of the product to which they relate."

Claims

1. A method for searching for compounds or mutations interacting directly or indirectly with the insulin signaling pathway, characterized in that a viable chico mutant insect is treated with at least one compound or with at least one mutation generating means, and that the effect of such treatment on the body size and/or cell size and/or development time and/or lipid level is determined whereby alterations of the body size and/or cell size and/or development time and/or lipid level are detectable in at least part of the animal.

2. The method of claim 1 characterized in that the viable chico mutant insect comprises at most one wild-type chico gene.

3. The method of claim 2 wherein the mutant is a Drosophila mutant and wherein said mutant is treated in the egg or larvae stadium with said compound or compound generating means.

4. The method of claim 2 or 3 wherein the mutant does not comprise a wild-type chico gene.

5. The method of claim 2 or 3 wherein the Drosophila mutant comprises one wild-type chico gene.

6. The method of claim 5 wherein the wild-type chico gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).

7. The method of claim 6, wherein the wild-type chico gene is the genomic or the cDNA sequence represented in Table 1 (SEQ. ID. NO. 1, 2) or Table 2 (SEQ. ID. NO. 4).

8. The method of anyone of claims 2 to 7 wherein the Drosophila mutant comprises at least one chico mutation with lacking or reduced activity compared to wild-type chico.

9. The method of claim 7 wherein the chico mutation is the mutation described in Figure 3A.

AMENDED SHEET

10. The method of anyone of claims 2 to 9
wherein the *Drosophila* lacks at least one *chico* gene.

11. The method of claim 10 wherein the mutant
lacks both *chico* genes.

5 12. The method of anyone of claims 1 to 11
wherein the compound is a compound for the treatment of
diabetes type 2.

10 13. The method of anyone of claims 1 to 12,
wherein the alteration of the body size and/or the cell
size and/or the development time and/or the lipid level
is detectable in the whole animal.

15 14. The method of anyone of claims 1 to 12,
wherein the alteration of the body size and/or the cell
size and/or the development time and/or the lipid level
is detectable in the head region only.

15 15. A viable insect mutant comprising at most
one wild-type *chico* gene in at least a part of its body
and said at least one part of the body shows reduced
size.

20 16. The mutant of claim 15 that does not
comprise as sole *chico* genes two *chico*¹ genes.

17. The mutant of claim 15 or 16 that does
not comprise a wild-type *chico* gene.

25 18. The mutant of claim 15 or 16 that
comprises one wild-type *chico* gene.

19. The mutant of claim 18 wherein the wild-
type *chico* gene encodes the amino acid sequence of Table
1 (SEQ. ID. NO. 2, 3).

20 20. The mutant of claim 19, wherein the wild-
type *chico* gene is the genomic or the cDNA sequence
represented in Table 2 (SEQ. ID. NO. 4) or Table 1 (SEQ.
ID. NO. 1, 2).

25 21. The mutant of anyone of claims 15 to 20
comprising at least one *chico* mutation with lacking or
reduced activity compared to wild-type *chico*.

35 22. The mutant of claim 21 wherein the *chico*
mutation is the mutation described in Figure 3A.

23. The mutant of anyone of claims 15 to 22 lacking at least one chico gene.

24. The mutant of claim 15 lacking both chico genes.

5 25. The mutant of anyone of claims 15 to 24 which is a fly mutant, in particular a Drosophila mutant.

26. The mutant of anyone of claims 15 to 25, wherein at most one wild-type chico gene is found in the whole body of the insect.

10 27. The mutant of anyone of claims 15 to 25, wherein at most one wild-type chico gene is found in the head region of the insect only.

15 28. Use of an insect according to anyone of claims 15 to 27 as a means in screening compounds for modulating diseases.

29. Use of an insect according to anyone of claims 15 to 27 as a means for searching for mutations involved directly or indirectly in the insulin signaling pathway.

20 30. Use according to claim 22 or 23, characterized in that the disease is diabetes type 2.

31. A method for generating a mutant insect, characterized in that adult animals, in particular males, are treated with a mutation generating means under 25 mutation generating conditions, that thus treated insects are crossed to wild-type or mutant insects, in particular chico mutant insects, and that viable offsprings with altered cell number and /or cell size and/or developmental time and/or lipid levels are cultivated 30 under suitable conditions.

PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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Vorderberg 11
8044 Zürich
SUISSE

10. OKT. 2001		V	N	I	
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1 10.10.01					
2 15.10. PK					

FAX: 0041 1 251 67 17

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 05.10.2001

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
02559PCInternational application No.
PCT/IB99/01166International filing date (day/month/year)
22/06/1999Priority date (day/month/year)
22/06/1999Applicant
UNIVERSITÄT ZÜRICH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

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For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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Authorized officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 02559PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB99/01166	International filing date (day/month/year) 22/06/1999	Priority date (day/month/year) 22/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant UNIVERSITÄT ZÜRICH et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 08/01/2001	Date of completion of this report 05.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lanzrein, M Telephone No. +49 89 2399 7358



INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/IB99/01166

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-44 as originally filed

Claims, No.:

1-31 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

Sequence listing part of the description, pages:

1-16, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB99/01166

the description, pages:

the claims, Nos.:

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N) Yes: Claims 1-14, 28-31
 No: Claims 15-27

Inventive step (IS) Yes: Claims 1-14, 28-31
 No: Claims 15-27

Industrial applicability (IA) Yes: Claims 1-31
 No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: Leevers, S. et al.: 'The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth.' EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594, XP000877417 EYNSHAM, OXFORD GB

D2: Berg C A; Spradling A C: Studies on the rate and site-specificity of p element transposition. GENETICS 127, 3, 515-524 (1991), cited in the application

D3: Riesgo-Escobar J. R. et al.: chico, a Drosophila homologue of mammalian insulin receptor substrate (IRS) genes, is required cell-autonomously for cell size. 39th Annual Drosophila Research Conference, 1998: 32, p. a12.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application relates to Drosophila mutants with reduced body or cell size. Mutations or null alleles of *chico* result in reduced body size. The *chico* gene product is a homologue of mammalian insulin receptor substrate (IRS) proteins. Mutant flies are thus useful in screening for compounds interacting with the insulin signalling pathway.
2. **Novelty (Art. 33 (2) PCT).**
 - 2.1 Claims 1-14, 28-31 appear to be novel over the cited prior art. Document D1 shows that ectopic expression of a dominant negative mutant of Dp110 (DP110^{D95A}) reduced cell size in the wings (Fig. 3) and eyes (Fig. 4) resulting in smaller wings and eyes. Since the claims are restricted to *chico* mutants, D1 does not affect novelty.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB99/01166

2.2 Claims 15-27 lack novelty over D2. As revealed in the description p. 3-4, *chico*¹ is a synonym for the P element induced mutation *fs(2)4*¹ disclosed in D2. The description states that "two further phenotypes associated with the defect *fs(2)4*¹ could be observed: Homozygous animals are reduced in size and adult flies have increased lipid levels". This statement unambiguously reveals that the genotypes of *fs(2)4*¹ and *chico* are the same. Accordingly, it appears that so far undiscovered (or never reported) phenotypic traits of *fs(2)4*¹ were found.

For assessment of novelty of the product claims, said phenotypic traits are of no relevance. Said traits represent non-distinctive characteristics which do not imply a particular form of the product. Since the known and claimed products are identical in all respects, an objection of novelty arises (cf PCT Guidelines Section IV: III-4.8 and IV-7.6).

The same applies with regards to the sequence data included in claims 6, 7.

As a consequence of the above, D2 is prejudicial to novelty of the product claims 15-27.

3. Inventive step (Art. 33(3) PCT).

Claims 1-14, 28-31 are considered to involve an inventive step within the meaning of Art. 33 (3) PCT.

Said claims concern screening methods using *chico* mutants.

The meeting abstract D3 describes the phenotype of *chico* mutants and reveals the function of the gene product as insulin receptor substrate. However, D3 does neither provide any information regarding the gene locus of *chico* nor does it make a link between *fs(2)4*¹ and *chico*. The information provided in D3 is therefore insufficient for the skilled person to generate *chico* mutants for use in the screening methods of said claims.

Thus, D3 is not an enabling disclosure and is therefore not considered relevant for evaluation of inventive step of claims.

Starting from D2, the skilled person would not have derived the phenotype of the reduced body size and therefore would not have considered the use of the mutant for the screening methods recited in claims 1-14, 28-31.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB99/01166

Re Item VIII

Certain observations on the international application

1. Claims 15-27 are unclear because the subject-matter for which protection is sought is not precisely defined.

In the present draft, claim 15 refers to an "insect mutant having at most one wild type *chico* gene". This can be understood as extending to insects having no *chico* gene at all, i.e. insects which naturally do not have the *chico* gene and have some mutation in another gene. Thus, claim 15 and appending claims 16-27 cover a large group of insect mutants, for which there is no support (Art. 6 PCT) and which is not unambiguously distinguishable from the prior art (Art. 6 and Art. 33 (2) PCT).

2. Claims 1, 2, 4, 5, 12-24, 26-31 are not supported by the description as required by Art. 6 PCT. Said claims refer to mutants of any insect, whereas the examples in the description concern *Drosophila* mutants only. The contribution of the present application clearly belongs to the field of *Drosophila* mutants and does not warrant broadening of the whole concept to all insects.

3. Claims 1-5, 8, 10-18, 21-31 refer to a *chico* mutant. The mutant *drosophila* or insect is specified solely by a name which, however, is meaningless to the person skilled in the art. Although the mutation has been described in the prior art, it has been given other names therein. It is therefore not clear what the subject matter is and the claims are not enabled (Art. 5/6 PCT).

The PCT Guidelines state in Section IV, II-4.16: "The use of proper names or similar words to refer to materials or articles is undesirable insofar as such words merely denote origin or where they relate to a range of different products. If such a word is used, then in order to satisfy the requirements of Article 5, the product must normally be sufficiently identified without reliance upon the word, to enable the invention to be carried out by a person skilled in the art. However, where such words have become internationally accepted as standard descriptive terms and have acquired a precise meaning (for example "Bowden" cable, "Bellville" washer), they may be allowed meaning (for example "Bowden" cable, "Bellville" washer), they may be allowed without further identification of the product to which they relate.".

Claims

1. A method for searching for compounds or mutations interacting directly or indirectly with the insulin signaling pathway, characterized in that a viable insect is treated with at least one compound or with at least one mutation generating means, and that the effect of such treatment on the body size and/or cell size and/or development time and/or lipid level is determined whereby alterations of the body size and/or cell size and/or development time and/or lipid level are detectable in at least part of the animal.

2. The method of claim 1 characterized in that the viable insect is a viable *chico* mutant insect, whereby said mutant comprises at most one wild-type *chico* gene.

3. The method of claim 2 wherein the mutant is a *Drosophila* mutant and wherein said mutant is treated in the egg or larvae stadium with said compound or compound generating means.

4. The method of claim 2 or 3 wherein the mutant does not comprise a wild-type *chico* gene.

5. The method of claim 2 or 3 wherein the *Drosophila* mutant comprises one wild-type *chico* gene.

6. The method of claim 5 wherein the wild-type *chico* gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).

7. The method of claim 6, wherein the wild-type *chico* gene is the genomic or the cDNA sequence represented in Table 1 (SEQ. ID. NO. 1, 2) or Table 2 (SEQ. ID. NO. 4).

8. The method of anyone of claims 2 to 7 wherein the *Drosophila* mutant comprises at least one *chico* mutation with lacking or reduced activity compared to wild-type *chico*.

9. The method of claim 7 wherein the *chico* mutation is the mutation described in Figure 3A.

10. The method of anyone of claims 2 to 9
wherein the *Drosophila* lacks at least one *chico* gene.

11. The method of claim 10 wherein the mutant
lacks both *chico* genes.

5 12. The method of anyone of claims 1 to 11
wherein the compound is a compound for the treatment of
diabetes type 2.

10 13. The method of anyone of claims 1 to 12,
wherein the alteration of the body size and/or the cell
size and/or the development time and/or the lipid level
is detectable in the whole animal.

15 14. The method of anyone of claims 1 to 12,
wherein the alteration of the body size and/or the cell
size and/or the development time and/or the lipid level
is detectable in the head region only.

15. A viable insect mutant comprising at most
one wild-type *chico* gene in at least a part of its body.

16. The mutant of claim 15 that does not
comprise as sole *chico* genes two *chico*¹ genes.

20 17. The mutant of claim 15 or 16 that does
not comprise a wild-type *chico* gene.

18. The mutant of claim 15 or 16 that
comprises one wild-type *chico* gene.

25 19. The mutant of claim 18 wherein the wild-
type *chico* gene encodes the amino acid sequence of Table
1 (SEQ. ID. NO. 2, 3).

20 20. The mutant of claim 19, wherein the wild-
type *chico* gene is the genomic or the cDNA sequence
represented in Table 2 (SEQ. ID. NO. 4) or Table 1 (SEQ.
30 ID. NO. 1, 2).

21. The mutant of anyone of claims 15 to 20
comprising at least one *chico* mutation with lacking or
reduced activity compared to wild-type *chico*.

35 22. The mutant of claim 21 wherein the *chico*
mutation is the mutation described in Figure 3A.

23. The mutant of anyone of claims 15 to 22
lacking at least one *chico* gene.

24. The mutant of claim 15 lacking both *chico* genes.

25. The mutant of anyone of claims 15 to 24 which is a fly mutant, in particular a *Drosophila* mutant.

5 26. The mutant of anyone of claims 15 to 25, wherein at most one wild-type *chico* gene is found in the whole body of the insect.

10 27. The mutant of anyone of claims 15 to 25, wherein at most one wild-type *chico* gene is found in the head region of the insect only.

28. Use of an insect according to anyone of claims 15 to 27 as a means in screening compounds for modulating diseases.

15 29. Use of an insect according to anyone of claims 15 to 27 as a means for searching for mutations involved directly or indirectly in the insulin signaling pathway.

30. Use according to claim 22 or 23, characterized in that the disease is diabetes type 2.

20 31. A method for generating a mutant insect, characterized in that adult animals, in particular males, are treated with a mutation generating means under mutation generating conditions, that thus treated insects are crossed to wild-type or mutant insects, in particular 25 *chico* mutant insects, and that viable offsprings with altered cell number and /or cell size and/or developmental time and/or lipid levels are cultivated under suitable conditions.

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Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 00/78940 A1

(54) Title: IN VIVO INSECT MODEL SYSTEM FOR TYPE-2 DIABETES

(57) Abstract: An in vivo monitor system for e.g. investigating defects in the insulin signaling pathway and screening for drugs suitable for the treatment of such defects, in particular a system using Drosophila chico mutants, is disclosed as well as a method for using such a system and for its generation.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/IB 99/01166A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/00 C07K14/435 A01K67/033

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LEEVERS, S. ET AL.: "The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth." EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594, XP000877417 EYNSHAM, OXFORD GB the whole document ---	1
Y	US 4 774 321 A (ROSNER MARSHA R ET AL) 27 September 1988 (1988-09-27) the whole document ---	1 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 March 2000

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28/03/2000

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INTERNATIONAL SEARCH REPORT

Intell. Prop. Application No
PCT/IB 99/01166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THE I, HANNIGAN GE, COWLEY GS, REGINALD S, ZHONG Y, GUSELLA JF, HARIHARAN IK, BERNARDS A. : "Rescue of a Drosophila NF1 mutant phenotype by protein kinase A." SCIENCE. , vol. 276, no. 5313, 2 May 1997 (1997-05-02), pages 791-794, XP000877265 the whole document ---	1
Y	WO 99 05258 A (ARCH DEV CORP ;UNIV CALIFORNIA (US)) 4 February 1999 (1999-02-04) claims 22-24 ---	1
A	LEROITH D: "A novel Drosophila insulin receptor: fly in the ointment or evolutionary conservation?" ENDOCRINOLOGY. 1995 JUN;136(6):2355-6. , vol. 136, no. 6, June 1995 (1995-06), pages 2355-2356, XP000884907 the whole document ---	1
T	BOHNI R, RIESGO-ESCOVAR J, OLDMHAM S, BROGIOLO W, STOCKER H, ANDRUSS BF, BECKINGHAM K, HAFEN E. : "Autonomous control of cell and organ size by CHICO, a Drosophila homolog of vertebrate IRS1-4." CELL. , vol. 97, no. 7, 25 June 1999 (1999-06-25), pages 865-875, XP000877263 the whole document ---	1-31
T	EDGAR BA. : "From small flies come big discoveries about size control." NAT CELL BIOL. 1999 DEC;1(8):E191-E193., XP000889763 the whole document ---	1
T	LEEVERS SJ.: "Perspectives: cell biology. All creatures great and small." SCIENCE, vol. 285, no. 5436, 24 September 1999 (1999-09-24), pages 2082-2083, XP000877264 the whole document ---	1
T	WEINKOVE D, LEEVERS SJ. : "The genetic control of organ growth: insights from Drosophila." CURR OPIN GENET DEV. , vol. 10, no. 1, February 2000 (2000-02), pages 75-80, XP000889771 the whole document ---	1
		-/-

INTERNATIONAL SEARCH REPORT

Intern'l Application No

PCT/IB 99/01166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOLZ L ET AL: "CPK IS A NOVEL CLASS OF DROSOPHILA PTDINS 3-KINASE CONTAINING A C2 DOMAIN" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, VOL. 271, NO. 23, 7 June 1996 (1996-06-07), pages 13892-13899, XP002073709 ISSN: 0021-9258 -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01166

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1 to 14 are directed to a method of treatment of the animal body, the search has been carried out and based on the alleged effects of the animal.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/IB 99/01166

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 4774321	A 27-09-1988	NONE		
WO 9905258	A 04-02-1999	AU 8408298	A	16-02-1999

10/019,098

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REC'D 27 FEB 2002

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 02559PC	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB99/01166	International filing date (day/month/year) 22/06/1999	Priority date (day/month/year) [22/06/1999]	
International Patent Classification (IPC) or national classification and IPC C12N15/00			
Applicant UNIVERSITÄT ZÜRICH et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 08/01/2001	Date of completion of this report 11.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lanzrein, M Telephone No. +49 89 2399 7358



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB99/01166

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-44 as originally filed

Claims, No.:

1-31 as received on 30/08/2001 with letter of 29/08/2001

Drawings, sheets:

1/8-8/8 as originally filed

Sequence listing part of the description, pages:

1-16, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB99/01166

the description, pages:

the claims, Nos.:

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-14, 28-31
No: Claims 15-27

Inventive step (IS) Yes: Claims 1-14, 28-31
No: Claims 15-27

Industrial applicability (IA) Yes: Claims 1-31
No: Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: Leevers, S. et al.: 'The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth.' EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594, XP000877417 EYNSHAM, OXFORD GB

D2: Berg C A; Spradling A C: Studies on the rate and site-specificity of p element transposition. GENETICS 127, 3, 515-524 (1991), cited in the application

D3: Riesgo-Escobar J. R. et al.: chico, a Drosophila homologue of mammalian insulin receptor substrate (IRS) genes, is required cell-autonomously for cell size. 39th Annual Drosophila Research Conference, 1998: 32, p. a12.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application relates to Drosophila mutants with reduced body or cell size. Mutations or null alleles of *chico* result in reduced body size. The *chico* gene product is a homologue of mammalian insulin receptor substrate (IRS) proteins. Mutant flies are thus useful in screening for compounds interacting with the insulin signalling pathway.
2. **Novelty (Art. 33 (2) PCT).**
 - 2.1 Claims 1-14, 28-31 appear to be novel over the cited prior art. Document D1 shows that ectopic expression of a dominant negative mutant of Dp110 (DP110^{D954A}) reduced cell size in the wings (Fig. 3) and eyes (Fig. 4) resulting in smaller wings and eyes. Since the claims are restricted to *chico* mutants, D1 does not affect novelty.

2.2 Claims 15-27 lack novelty over D2. As revealed in the description p. 3-4, *chico*¹ is a synonym for the P element induced mutation *fs(2)4*¹ disclosed in D2. The description states that "two further phenotypes associated with the defect *fs(2)4*¹ could be observed: Homozygous animals are reduced in size and adult flies have increased lipid levels". This statement unambiguously reveals that the genotypes of *fs(2)4*¹ and *chico* are the same. Accordingly, it appears that so far undiscovered (or never reported) phenotypic traits of *fs(2)4*¹ were found.

For assessment of novelty of the product claims, said phenotypic traits are of no relevance. Said traits represent non-distinctive characteristics which do not imply a particular form of the product. Since the known and claimed products are identical in all respects, an objection of novelty arises (cf PCT Guidelines Section IV: III-4.8 and IV-7.6).

The same applies with regards to the sequence data included in claims 6, 7.

As a consequence of the above, D2 is prejudicial to novelty of the product claims 15-27.

3. Inventive step (Art. 33(3) PCT).

Claims 1-14, 28-31 are considered to involve an inventive step within the meaning of Art. 33 (3) PCT.

Said claims concern screening methods using *chico* mutants.

The meeting abstract D3 describes the phenotype of *chico* mutants and reveals the function of the gene product as insulin receptor substrate. However, D3 does neither provide any information regarding the gene locus of *chico* nor does it make a link between *fs(2)4*¹ and *chico*. The information provided in D3 is therefore insufficient for the skilled person to generate *chico* mutants for use in the screening methods of said claims.

Thus, D3 is not an enabling disclosure and is therefore not considered relevant for evaluation of inventive step of claims.

Starting from D2, the skilled person would not have derived the phenotype of the reduced body size and therefore would not have considered the use of the mutant for the screening methods recited in claims 1-14, 28-31.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB99/01166

Re Item VIII

Certain observations on the international application

1. Claims 15-27 are unclear because the subject-matter for which protection is sought is not precisely defined.
In the present draft, claim 15 refers to an "insect mutant having at most one wild type *chico* gene". This can be understood as extending to insects having no *chico* gene at all, i.e. insects which naturally do not have the *chico* gene and have some mutation in another gene. Thus, claim 15 and appending claims 16-27 cover a large group of insect mutants, for which there is no support (Art. 6 PCT) and which is not unambiguously distinguishable from the prior art (Art. 6 and Art. 33 (2) PCT).
2. Claims 1, 2, 4, 5, 12-24, 26-31 are not supported by the description as required by Art. 6 PCT. Said claims refer to mutants of any insect, whereas the examples in the description concern *Drosophila* mutants only. The contribution of the present application clearly belongs to the field of *Drosophila* mutants and does not warrant broadening of the whole concept to all insects.
3. Claims 1-5, 8, 10-18, 21-31 refer to a *chico* mutant. The mutant *drosophila* or insect is specified solely by a name which, however, is meaningless to the person skilled in the art. Although the mutation has been described in the prior art, it has been given other names therein. It is therefore not clear what the subject matter is and the claims are not enabled (Art. 5/6 PCT).
The PCT Guidelines state in Section IV, II-4.16: "The use of proper names or similar words to refer to materials or articles is undesirable insofar as such words merely denote origin or where they relate to a range of different products. If such a word is used, then in order to satisfy the requirements of Article 5, the product must normally be sufficiently identified without reliance upon the word, to enable the invention to be carried out by a person skilled in the art. However, where such words have become internationally accepted as standard descriptive terms and have acquired a precise meaning (for example "Bowden" cable, "Bellville" washer), they may be allowed meaning (for example "Bowden" cable, "Bellville" washer), they may be allowed without further identification of the product to which they relate.".

Claims

1. A method for searching for compounds or mutations interacting directly or indirectly with the 5 insulin signaling pathway, characterized in that a viable chico mutant insect is treated with at least one compound or with at least one mutation generating means, and that the effect of such treatment on the body size and/or cell size and/or development time and/or lipid level is 10 determined whereby alterations of the body size and/or cell size and/or development time and/or lipid level are detectable in at least part of the animal.

2. The method of claim 1 characterized in that the viable chico mutant insect comprises at most one 15 wild-type *chico* gene.

3. The method of claim 2 wherein the mutant is a *Drosophila* mutant and wherein said mutant is treated in the egg or larvae stadium with said compound or compound generating means.

20 4. The method of claim 2 or 3 wherein the mutant does not comprise a wild-type *chico* gene.

5. The method of claim 2 or 3 wherein the *Drosophila* mutant comprises one wild-type *chico* gene.

6. The method of claim 5 wherein the wild- 25 type *chico* gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).

7. The method of claim 6, wherein the wild-type *chico* gene is the genomic or the cDNA sequence represented in Table 1 (SEQ. ID. NO. 1, 2) or Table 2 30 (SEQ. ID. NO. 4).

8. The method of anyone of claims 2 to 7 wherein the *Drosophila* mutant comprises at least one *chico* mutation with lacking or reduced activity compared to wild-type *chico*.

35 9. The method of claim 7 wherein the *chico* mutation is the mutation described in Figure 3A.

10. The method of anyone of claims 2 to 9 wherein the *Drosophila* lacks at least one *chico* gene.
11. The method of claim 10 wherein the mutant lacks both *chico* genes.
- 5 12. The method of anyone of claims 1 to 11 wherein the compound is a compound for the treatment of diabetes type 2.
- 10 13. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell size and/or the development time and/or the lipid level is detectable in the whole animal.
- 15 14. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell size and/or the development time and/or the lipid level is detectable in the head region only.
15. A viable insect mutant comprising at most one wild-type *chico* gene in at least a part of its body and said at least one part of the body shows reduced size.
- 20 16. The mutant of claim 15 that does not comprise as sole *chico* genes two *chico*¹ genes.
17. The mutant of claim 15 or 16 that does not comprise a wild-type *chico* gene.
- 25 18. The mutant of claim 15 or 16 that comprises one wild-type *chico* gene.
19. The mutant of claim 18 wherein the wild-type *chico* gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).
- 20 20. The mutant of claim 19, wherein the wild-type *chico* gene is the genomic or the cDNA sequence represented in Table 2 (SEQ. ID. NO. 4) or Table 1 (SEQ. ID. NO. 1, 2).
- 35 21. The mutant of anyone of claims 15 to 20 comprising at least one *chico* mutation with lacking or reduced activity compared to wild-type *chico*.
22. The mutant of claim 21 wherein the *chico* mutation is the mutation described in Figure 3A.

23. The mutant of anyone of claims 15 to 22 lacking at least one *chico* gene.

24. The mutant of claim 15 lacking both *chico* genes.

5 25. The mutant of anyone of claims 15 to 24 which is a fly mutant, in particular a *Drosophila* mutant.

26. The mutant of anyone of claims 15 to 25, wherein at most one wild-type *chico* gene is found in the whole body of the insect.

10 27. The mutant of anyone of claims 15 to 25, wherein at most one wild-type *chico* gene is found in the head region of the insect only.

15 28. Use of an insect according to anyone of claims 15 to 27 as a means in screening compounds for modulating diseases.

29. Use of an insect according to anyone of claims 15 to 27 as a means for searching for mutations involved directly or indirectly in the insulin signalling pathway.

20 30. Use according to claim 22 or 23, characterized in that the disease is diabetes type 2.

31. A method for generating a mutant insect, characterized in that adult animals, in particular males, are treated with a mutation generating means under 25 mutation generating conditions, that thus treated insects are crossed to wild-type or mutant insects, in particular *chico* mutant insects, and that viable offsprings with altered cell number and /or cell size and/or developmental time and/or lipid levels are cultivated 30 under suitable conditions.

PATENT COOPERATION TREATY
PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 02559PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/IB 99/ 01166	International filing date (day/month/year) 22/06/1999	(Earliest) Priority Date (day/month/year)
Applicant UNIVERSITÄT ZÜRICH et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

IN VIVO INSECT MODEL SYSTEM FOR TYPE-2 DIABETES

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01166

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1 to 14 are directed to a method of treatment of the animal body, the search has been carried out and based on the alleged effects of the animal.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01166

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

An in vivo monitor system for e.g. investigating defects in the insulin signaling pathway and screening for drugs suitable for the treatment of such defects, in particular a system using *Drosophila chico* mutants, is disclosed as well as a method for using such a system and for its generation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01166A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/00 C07K14/435 A01K67/033

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LEEVERS, S. ET AL.: "The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth." EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594, XP000877417 EYNSHAM, OXFORD GB the whole document ---	1
Y	US 4 774 321 A (ROSNER MARSHA R ET AL) 27 September 1988 (1988-09-27) the whole document ---	1 -/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the International search

10 March 2000

Date of mailing of the International search report

28/03/2000

Name and mailing address of the ISA
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Authorized officer

Chambonnet, F

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/01166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THE I, HANNIGAN GE, COWLEY GS, REGINALD S, ZHONG Y, GUSELLA JF, HARIHARAN IK, BERNARDS A. : "Rescue of a Drosophila NF1 mutant phenotype by protein kinase A." SCIENCE. , vol. 276, no. 5313, 2 May 1997 (1997-05-02), pages 791-794, XP000877265 the whole document ---	1
Y	WO 99 05258 A (ARCH DEV CORP ;UNIV CALIFORNIA (US)) 4 February 1999 (1999-02-04) claims 22-24 ---	1
A	LEROITH D: "A novel Drosophila insulin receptor: fly in the ointment or evolutionary conservation?" ENDOCRINOLOGY. 1995 JUN;136(6):2355-6. , vol. 136, no. 6, June 1995 (1995-06), pages 2355-2356, XP000884907 the whole document ---	1
T	BOHNI R, RIESGO-ESCOVAR J, OLDHAM S, BROGIOLI W, STOCKER H, ANDRUSS BF, BECKINGHAM K, HAFEN E. : "Autonomous control of cell and organ size by CHICO, a Drosophila homolog of vertebrate IRS1-4." CELL. , vol. 97, no. 7, 25 June 1999 (1999-06-25), pages 865-875, XP000877263 the whole document ---	1-31
T	EDGAR BA. : "From small flies come big discoveries about size control." NAT CELL BIOL. 1999 DEC;1(8):E191-E193., XP000889763 the whole document ---	1
T	LEEVERS SJ.: "Perspectives: cell biology. All creatures great and small." SCIENCE, vol. 285, no. 5436, 24 September 1999 (1999-09-24), pages 2082-2083, XP000877264 the whole document ---	1
T	WEINKOVE D, LEEVERS SJ. : "The genetic control of organ growth: insights from Drosophila." CURR OPIN GENET DEV. , vol. 10, no. 1, February 2000 (2000-02), pages 75-80, XP000889771 the whole document ---	1

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/01166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOLZ L ET AL: "CPK IS A NOVEL CLASS OF DROSOPHILA PTDINS 3-KINASE CONTAINING A C2 DOMAIN" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 271, no. 23, 7 June 1996 (1996-06-07), pages 13892-13899, XP002073709 ISSN: 0021-9258 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/18 99/01166

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4774321	A 27-09-1988	NONE	
WO 9905258	A 04-02-1999	AU 8408298 A	16-02-1999